In the specification:

Page 30, line 12, change "weight reduction weight" to – weight reduction –.

Page 33, line 17, change "(200-250) grams" to – (200-250 grams) –.

In the claims:

1. (Twice Amended) A method of treating obesity in a human subject comprising administering to said subject an effective amount of a composition comprising an anti-obesity agent consisting of an amylin or an amylin agonist and a pharmaceutically acceptable carrier.

REMARKS

Applicants have carefully considered the Examiner's June 24, 1999 Office Action, and provide the following remarks. Claims 1 through 6 are pending in the application. Claim 1 has been amended. Support for the amendment is found throughout the specification, for example at pages 1, 12, 13, and 25-28, and no new matter has been added. This Response is not intended to limit, does not limit, and may not be construed as limiting the appropriate scope of protection provided under the doctrine of equivalents. The doctrine of equivalents should be applied to the fullest extent to protect Applicants from those who may misappropriate their invention by using and/or commercializing subject matter that is not substantially different from the claimed inventions. *See Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1521-22, 35 USPQ2d 1641, 1648 (Fed. Cir. 1995) (en banc), *rev'd on other grounds*, *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 41 USPQ2d 1865 (1997).

Applicants submit this Response in compliance with 37 CFR § 1.116 and respectfully request entry of the amendments and reconsideration of the Final Office Action mailed June 24, 1999.

Objection

Applicants have amended the specification to correct the typographical errors observed by the Examiner and ask that the objection now be withdrawn.

Withdrawn § 112 Rejection

The Examiner has withdrawn the rejection of pending claims 1-6 under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled with regard to the scope, "for a method of 'preventing' obesity in a human subject" (June 24, 1999 Office Action at page 2).

Rejections Maintained

35 USC § 102(e)

The Examiner maintained the rejection of claims 1-3 under 35 U.S.C. § 102(e) as allegedly anticipated by Rink *et al.*, U.S. Patent No. 5,739,106, issued on April 14, 1998, for "Appetite Regulating Compositions" on application filed June 7, 1995.

The Examiner states that this § 102 rejection was maintained on the assertion that:

> the claims, as currently drafted, use the open claim language "comprising" and do not exclude the administration of any other substance other than amylin or amylin agonist. Claims 83-85 [of Rink *et al.*] do encompass methods for control of body

> weight or control of appetite or suppression of food intake in a mammal comprising administering an effective amount of an amylin agonist, in particular ^{25,28,29}pro-h-amylin. Amylin agonist is administered in an amount of about 0.1 μg/kg/day (column 95, lines 1-8) and 1-3 times a day (see column 21, lines 26 and 27) The amylin agonist can be s-calcitonin or h-amylin (see column 8, lines 35-38). further, Rink *et al.* ('106) illustrate that administration of amylin alone did suppress food intake (see Figure 1). Rink *et al.* also discuss the art-recognized fact that amylin reduces food intake significantly in mammals (see paragraph bridging columns 6 and 7) [June 24, 1999 Office Action, page 2].

Applicants respectfully traverse the rejection to the extent that it may be held to apply to the present claims, none of which – either as originally filed, as previously amended, or as amended by this Response – are anticipated by this reference.

35 U.S.C. § 102 provides, in pertinent part that a "person shall be entitled to a patent unless . . . (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, ..." A claim is anticipated and thus not novel within the meaning of Section 102 only if it can be proved that a single prior art reference discloses each element of the claimed invention. *E.g., In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("[T]he [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." (citations omitted)). When the claim in issue is directed to a process, as in the instant case, anticipation requires identity of the claimed process and the process of the prior art. Thus, the claimed process, including each step of the process, must be described or embodied in a single reference. *Glaverbel Societe Anonyme v. Northlake Marketing*, 45 F.3d 1550, 1554, 33 USPQ2d 1496, 1498 (Fed. Cir. 1995).

As previously pointed out to the Examiner, whether or not § 102(e) may be applied against Applicants' invention, it is clear that Rink *et al.* does not describe the methods of treating obesity claimed in the instant application. Rink *et al.* is directed to (1) a composition that includes an amylin agonist admixed with a cholecystokinin ("CCK") agonist or (2) a composition that includes a hybrid peptide that incorporates features of amylin agonist peptides and CCK agonist peptides. The basis for the Rink *et al.* invention is not the use of amylin or an amylin agonist as a food intake inhibitor. To the contrary, Rink *et al.* set out the basis for their invention in the Summary of the Invention at Column 7 of the '106 patent, where they report that injection of 1μg/kg of amylin had no effect on food intake. Rink *et al.* state:

> Applicants have discovered that amylin agonists and CCK agonists when administered together, have a synergistic effect on reduction of food intake. The present application describes the use of an amylin agonist in conjunction with a CCK agonist for the control of food intake. For example, an IP injection of 1.0 μg/kg CCK-8 or of 1.0 μg/kg rat amylin has no measurable effect on food intake. But administration of 0.1 μg/kg of each peptide causes a substantial reduction of food intake about equivalent to that seen with 100 μg/kg of either peptide alone ['106 patent, column 7, lines 14-23; emphasis added].

The instant application, on the other hand, describes and claims the use of amylin or amylin agonists alone in the treatment or prevention of obesity in a human subject. The application describes the use, for example, of amylin or amylin agonist doses in the range of 30 μg to 300 μg. *See* pending claim 6, which reads, "A method according to claim 5 wherein said amylin or amylin agonist is administered in an amount from 30 μg/dose to 300 μg/dose."[1] Given that the

[1] Claim 5 is directed to the treatment or prevention of obesity by the subcutaneous administration of an amylin or amylin agonist from 1 to 4 times per day.

average adult human weighs about 70 kg, the instant application thus teaches that effective doses of an amylin or an amylin agonist alone for the treatment or prevention obesity in such subjects range from about 0.43 to about 4.3 μg/kg. Conversely, Rink *et al.* reports that a 1.0 μg/kg dose (equivalent to about 70μg/dose in an adult human) had no effect on food intake. In fact, Rink *et al.* reports that the preferred synergistic doses of CCK combined with an amylin agonist (0.1 μg/kg of each peptide) were those "equivalent to that seen with 100 μg/kg [a 7000 μg dose in an 70 kg adult human] of either peptide alone." In sum, Rink *et al.* provides that amylin and amylin agonists administered as described and claimed in the instant treatment of obesity application have "no measurable effect" on food intake, let alone obesity. Applicants thus submit that Rink *et al.* does not within the meaning of 35 USC § 102 teach the use of an amylin agonist alone for controlling appetite. Nor does it describe treating obesity in human subjects as set forth in the pending claims within the meaning of 35 USC § 102 and the anticipation rejection cannot stand.[2] Applicants request that the rejection be reconsidered and withdrawn.

35 USC § 103

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[2] The Examiner states that claims 83-85 of Rink *et al.* encompass methods for control of body weight in a mammal comprising administering a therapeutically effective amount of an amylin agonist such as $^{25, 28, 29}$pro-h-amylin. As previously pointed out, none of these claims refer to the administration of an amylin agonist alone. Claims 83-85 each refer to the administration of a composition of "any of claims 1-6, 17, 18, 32, 33, 46, 47, 61, 63 or 72," all of which are directed to compositions that comprise an amylin agonist and a CCK agonist admixed together (claims 1-6), to hybrid peptides comprising covalently linked amylin agonist and CCK agonist peptides (claims 17, 18, 32, 33, 46, 47, and 61), or to other specific hybrid peptides (claims 63 and 72).

The Examiner has also maintained the rejection of Claims 4-6 under 35 U.S.C. § 103(a) as allegedly unpatentable over Rink *et al.* as applied to claim 1 above, and further in view of Gaeta *et al.* (U.S. Patent No. 5,686,411, issued November 11, 1997 for "Amylin Agonist Peptides and Uses Therefor"). Applicants respectfully traverse the rejection to the extent that it may be held to apply to the present claims.

The Gaeta '411 patent specifically discloses and claims the amylin agonist $^{25, 28, 29}$Pro-h-amylin. In general it is directed to various amylin agonist peptides, including $^{25, 28, 29}$Pro-h-amylin, useful in the treatment of diabetes. The Examiner has acknowledged in a previous Office Action (mailed September 16, 1998) that, "Rink *et al.* do not teach the specific doses, times and route of administration recited in Claims 4-6." The Gaeta *et al.* patent, however, does not supply what Rink *et al.* lacks. Gaeta *et al.* does not contain any discussion of obesity or the treatment of obesity. Thus, the Examiner's reliance on Gaeta *et al.* as teaching various doses of amylin agonist compounds for the treatment of obesity is misplaced.

It is insufficient under the law to rely merely upon statements in a diabetes treatment composition patent regarding the ability of medical practitioners to determine the optimum dosage for their patients with diabetes. Gaeta *et al.* provides that, "For use by the physician, the compositions will be provided in dosage unit form containing an amount of an agonist compound with or without insulin or glucagon which will be effective in one or multiple doses to control or reestablish blood sugar at the selected level" (Column 8, lines 37-41). The instant invention is not directed to the control of blood glucose levels like Gaeta *et al.*, but to the treatment of obesity. Applicants also note that Gaeta *et al.* does not, as stated by the Examiner at page 3 of

the June 24, 1999 Office Action, report that "specific doses of amylin agonist at the frequencies and by routes of administration as recited in claims 4-6 have been safely administered to patients." Gaeta *et al.* does not, in fact, report on the *in vivo* testing of any amylin agonist compound in humans or animals. It does not, furthermore, provide any suggestion on the use of amylin or amylin agonists for treatment of obesity. Accordingly, the Gaeta *et al.* amylin agonist compound/treatment of diabetes patent does not supply what Rink *et al.* lacks, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

The Examiner also maintained the rejection of Claims 1-6 under 35 U.S.C. § 103(a) as allegedly unpatentable over Kolterman *et al.* (I) or Kolterman *et al.* (II) or Moyses *et al.* or Thompson *et al.* in view of Cooper *et al.* and Rink *et al.* As previously noted, these additional articles relate to methods of treating patients with diabetes mellitus by administration of amylin agonists, in particular [25, 28, 29] Pro-h-amylin, which has been the subject of numerous clinical trials over the last several years, and has now completed final phase 3 clinical testing by Amylin Pharmaceuticals.

The Examiner acknowledged in the previous Office Action, in fact, that "Kolterman *et al.* [I] or Kolterman et al [II] or Moyses *et al.* do not teach a method of treating or preventing obesity by administering pramlintide to a human subject." Applicants also pointed out that Dr. Cooper, co-founder of Amylin Pharmaceuticals and discoverer of the amylin molecule, subsequently invented and patented methods for treating obesity using amylin antagonists (U.S. Patent Nos. 5,364,841 and 5,280,014 issued to Cooper and Greene (the other co-founder of Amylin Pharmaceuticals) on January 18 and November 15, 1994, respectively, for "Treatment of

Obesity and Essential Hypertension and Related Disorders"). As described and claimed in the Cooper and Greene '841 and '014 patents, the treatment of obesity is by the administration of antagonists and blockers of amylin, and is not by the use of amylin or amylin agonists as described in the instant application. Thus, these patents teach away from the subject matter claimed herein.

The Examiner responded by declaring all this irrelevant. He states at pages 4-5 of the June 24, 1999 Office Action:

> Applicants argue that the cited references relate to methods of treating patients with diabetes mellitus and not of obesity. Applicants contend that Dr. Cooper is the co-founder of Amylin Pharmaceutics and the discoverer of amylin. Applicants further discuss patents, US 5,364,841, US 5,280,014 and US 5,656,590, on treatment of obesity and anorexia and state that these patents teach away from the subject matter claimed in the instant application.
>
> Applicants argument has been considered but is not found to be persuasive. First, none of the three patents mentioned by Applicants as teaching away from the instant invention were cited in the rejection claims 1-6 made in paragraph 10 of the Office Action mailed 09/16/98 (paper no. 8) under 35 U.S.C. § 103(a). Who discovered amylin is also not the issue. At issue is whether the claimed method is obvious over the prior-art methods, given the teachings of Kolterman *et al.*(I) or Kolterman *et al.* (II) or Moyses *et al.* or Thompson *et al.* in view of Cooper *et al.* and Rink *et al.* ('106) [emphases added].

In contrast to these statements, Applicants respectfully submit that the fact that the discoverer of amylin himself taught the use of amylin blockers for the treatment of obesity – the exact opposite of agonists as taught in the instant application – is of great moment in analyzing the Examiner's obviousness rejection. The fact that the Examiner only cited amylin agonist patents relating to the treatment of diabetes and did not cite treatment of obesity patents that are centered on the use of amylin antagonists is also of great importance. It is the law that any alleged reference "must

be read not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). The law further provides that it is clear error to find obviousness where alleged references "diverge from and teach away from the invention at hand." W. *L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984). Thus, contrary to the conclusions of the Examiner, these patents and the fact that the discover of amylin himself taught away from the use of agonists for the treatment of obesity – stating that amylin antagonists should be used instead – is highly probative of nonobviousness.

The Federal Circuit has often reminded that objective considerations of nonobviousness serve "as insurance against the insidious attraction of the siren hindsight." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d at 1553, 220 USPQ at 313. Indeed, according to the Court, "Evidence of secondary considerations may often be the most probative and cogent evidence [of nonobviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983). It is well known that one of the objective considerations that supports nonobviousness is the "failure of others." Here the evidence indicates that others, including Dr. Cooper – the discoverer of amylin and co-founder of Amylin Pharmaceuticals (the Company to which the instant application is assigned) – failed to discover to use of amylin agonists for treatment of obesity, and in fact proposed exactly the opposite. The patent law commands that, "Evidence that supports, rather than negates, patentability must be fairly considered." *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed.

Cir. 1988). It is submitted that this evidence, upon consideration, will be seen as providing a still further and important refutation of the Examiner's rejection.

Also teaching away from the obesity treatment described and claimed in the instant application is U.S. Patent No. 5,656,590, issued on August 12, 1997, to Rink *et al.* for "Treatment of Anexoria and Related States." "[I]n general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994), citing the United States Supreme Court decision and opinion in *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966) ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness"). The Rink '590 patent describes and claims methods for the treatment of patients suffering from anorexia or a similar condition by administering an amylin or an analog thereof in order to increase weight.

Thus, it will be seen that, in contrast to the Examiner's conclusion that it would have been obvious to use an amylin agonist to treat obesity, the art teaches the opposite. Amylin Pharmaceuticals, which for the last decade has been the world leader in the investigation and development of amylin and amylin agonist molecules for the treatment of human disorders, had itself determined that it was amylin antagonists rather than amylin agonists that would find utility in the treatment of obesity and that, in fact, the use of amylin agonists would lead to weight gain rather than weight decrease. *See* the '841 and '014 patents.

Applicants also note the following conclusions of the Examiner:

> As explained in paragraph 10 of the Office Action mailed 09/16/98 (paper no. 8), the invention as a whole, would have been obvious to a practitioner in view of the combined teachings of Kolterman *et al.* (I) or Kolterman *et al.* (II) or Moyses *et al.* or Thompson *et al.* in view of Cooper *et al.* and Rink *et al.* ('106), the contemporary knowledge in the art at the time of invention and the state of the art at the time of the invention. Given the close clinical association between type 2 diabetes and obesity as taught by Thompson *et al.*, Rink's explicit teaching that amylin agonists such as [25,28,29] pro-h-amylin is effective in controlling body weight, reducing food intake and suppressing appetite in humans, and the art-recognized clinical need for weight reduction in patients suffering from type II diabetes mellitus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's method (I and II) or Moyses' or Thompson's method of treatment for treating obesity in human subjects to produce the instant invention. Since weight reduction is often the recommended first course of action for patients suffering from type II diabetes mellitus as taught by Rink *et al.*, one of ordinary skill in the art would be motivated to produce the instant invention for the expected benefit of preventing NIDDM from advancing to or resulting in obesity. A skilled artisan would have had a reasonable expectation of success in using Kolterman's (I and II) or Moyses' or Thompson's method of treating type II diabetes also for treatment of obesity because these two associated clinical conditions share the common pathogenetic mechanisms as taught by Rink *et al.*

As noted above, the Rink *et al.* '106 CCK/amylin patent does not contain an "explicit teaching that amylin agonists such as [25,28,29] pro-h-amylin is effective in controlling body weight, reducing food intake and suppressing appetite in humans," as stated by the Examiner. Rather, it describes that such compounds are effective when combined with a CCK molecule. The further argument that because "weight reduction is often the recommended first course of action for patients suffering from type II diabetes mellitus as taught by Rink *et al.*, one of ordinary skill in the art would be motivated to produce the instant invention for the expected benefit of preventing NIDDM from advancing to or resulting in obesity," is circular and could only have been constructed in hindsight based upon the disclosures of the instant application. Applicants are not

aware of any statement in the documents relied on by the Examiner – most of which were co-authored by Applicant Kolterman – that suggest the inventions described and claimed in the instant application.

Indeed, Applicants submit that upon consideration of the lack of teaching in these documents, and upon consideration of the amylin antagonist and anorexia patents cited by Applicants that teach away from their inventions, coupled with a fuller understanding of the Rink *et al.* '106 CCK/amylin patent and the Gaeta *et al.* amylin agonist composition '411 patent, one is inescapably lead to a conclusion of nonobvious rather than obviousness as suggested by the Examiner. Applicants respectfully request that this § 103 rejection also be reconsidered and withdrawn.

New Rejections; Request to Withdraw Finality of Office Action

Applicants note the new rejections made in this Office Action. The Examiner has rejected Claims 1 and 2 under 35 U.S.C. § 102(e) as allegedly "anticipated by Cooper *et al.* (US 5,280,014) ('014) or Cooper *et al.* (US 5,364,841) ('841)" (June 24, 1999 Office Action, page 6). According to the Examiner,

> Cooper *et al.* ('014) teach a method of treating obesity in a subject comprising administering an effective amount of CGRP 8-37, which is an amylin agonist (see claims 1 and 11, and column 11, lines 3 and 4).
>
> Cooper *et al.* ('841) teach a method of treating obesity in a subject comprising administering an effective amount of CGRP 8-37, which is an amylin agonist (see claims 2 in combination with lines 7 and 8 of column 11) [emphases added].

Applicants respectfully traverse this rejection.

The rejection cannot stand at least for the reason that CGRP 8-37 is not an amylin agonist, as stated by the Examiner. CGRP 8-37 is an amylin antagonist. Thus, claim 2 of the '841 patent (cited by the Examiner in support of this new rejection) defines:

> 2. A method for the treatment of obesity in a subject comprising administering to said subject an amount of an amylin receptor antagonist effective to reduce amylin activity in said subject [emphasis added].

Similarly, claims 1 and 11 of the '014 patent (also cited by the Examiner in support of the new § 102 rejection) read:

> 1. A method for enhancing glycogen synthesis in a subject comprising administering to said subject an amount of an amylin antagonist effective to reduce amylin activity in said subject [emphasis added].
>
> 11. The method of any of claims 1, 2, 3 or 4 wherein said amylin antagonist comprises an anti-amylin antibody [emphasis added].

The '842 and '014 patents describe the use of amylin antagonists to treat obesity. They have no relevance to the claimed inventions for the treatment of obesity with an amylin or an amylin agonist, except to the extent that they support the patentability of the inventions claimed herein. Applicants respectfully request that this § 102 rejection of claims 1 and 2 also be reconsidered and withdrawn.[3]

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[3] *See also* U.S. Patent No. 5,260,275, issued to Cooper, *et al.* on November 9, 1993, for "Hypoglyemics." The Abstract of this patent, which issued on an application filed August 14, 1990, provides:

> Non-insulin dependent, or type 2, diabetes mellitus in a patient is treated by administering to the patient a hypoglycemic agent that enhances plasma concentrations of amylin and a therapeutically effective amount of an amylin antagonist. Hypoglycemic agents which enhance plasma concentrations of amylin can be sulfonylureas such as glibenclamide and tolbutamide. Amylin antagonists can be amylin 8-37 and **CGRP 8-37**. Administration of the amylin

Applicant also requests that the Examiner withdraw the finality of the June 24, 1999 Office Action. The Examiner asserted that "Applicants' amendment necessitated the new grounds of rejection presented in this Office Action." This is not understood. The amendment, while deemed by Applicants' to be neither necessary nor substantive in nature, was made at the request of the Examiner in order to speed prosecution. Furthermore, it is not understood how amending the claims from a "method of treating or preventing" to a "method of treating" as described in the application could have led the Examiner to, for example, any additional subject matter for review and analysis. Applicant thus requests that the Examiner reconsider and withdraw the finality of the Office Action.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance, and seek an early notice thereof. Should the Examiner have any remaining questions he is encouraged to

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antagonist in conjunction with the hypoglycemic agent also enhances the blood glucose lowering effects of the hypoglycemic agent.

telephone the undersigned so that they may be promptly resolved.

Respectfully submitted,

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